REMARKS

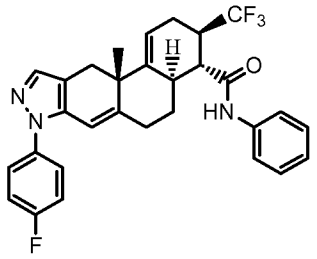
Status of Claims

Claims 1-4, 11-24 and 29-30 are pending in the application prior to the instant Amendment. Claim 24 is withdrawn from consideration. No claim is added, canceled or amended, leaving claims 1-4, 11-23 and 29-30 pending upon entry of the instant Response.

Restriction / Election

In response to the restriction requirement, Applicants hereby elect Group I, claims 1-4, 11-23 and 29-30, for further prosecution in this application. Applicants reserve the right to prosecute the non-elected claims in a continuation or divisional application.

In response to the requirement to elect species, Applicants hereby elect compound number 3 of claim 22 having the following structure as elected species for search purposes:



Claims readable thereon are 1-4, 11-19 and 22-23.

Information Disclosure Statement (IDS)

The Examiner stated that "unless the references have been cited by the examiner on form PTO-892, they have not been considered". (Office Action mailed May 1, 2009, page 7) Applicants respectfully request clarification.

Applicants point out that several references were submitted by the Applicants on Substitute for form 1449/PTO (not PTO-892) fully in compliance with 37 CFR 1.97 on March 11, 2005. It appears that the Examiner has considered these references as the Examiner has signed and dated (4/30/2009) the submitted IDS form. Applicants respectfully request clarification from the Examiner that all submitted references on form 1449 have been considered.

Co-pending Applications

To aid the Examiner with the examination of the instant application, Applicants bring the Examiner's attention to several pending applications that have at least one common inventor as the instant application:

11/904,186 (case # 21035YPCA),

10/551,933 (case # 21150P),

10/540,757 (case # 21158P), and

11/919,195 (case # 21877P).

Applicants point out that these co-pending applications may or may not be material to the patentability of the instant applicant. They are brought to the Examiner's attention merely for the convenience of the Examiner and for the thoroughness of disclosure (see MPEP 2004.9, 2004.10 and 2001.06(b)).

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 1-4, 11-23, 29 and 30 under 35 U.S.C. §103(a) as being obvious over Kumar et al. (J. Med. Chem., 1993, 36, 3278-3285; hereinafter, "Kumar"), Schane et al. (Steroids, 1985, 45(2), 171-85; hereinafter, "Schane") and Bell et al. (US 4,349,558; hereinafter, "Bell"). (Office Action mailed May 1, 2009, page 8) Applicants respectfully traverse this rejection as none of the cited references, either alone or in combination, provides any suggestion or motivation to a skilled artisan to select the right lead compounds and make the necessary modifications to arrive at the instant compounds.

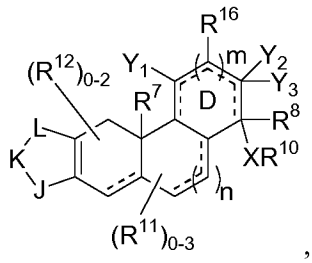
Courts have consistently held that a *prima facie* case of obviousness as related to a new chemical compound requires that the prior art provide some suggestion or motivation for making the specific molecular modifications necessary to achieve the claimed invention combined with a reasonable expectation of success. *Takeda v. Alphapharm*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). The court made it clear that "consistent with the legal principles enunciated in *KSR*", there must be "some reason that would have led a chemist to modify a known compound in a particular manner." *Id* at 1356-1357.

Moreover, the Federal Circuit case *Eisai* affirmed *Takeda* and further elaborated on the 103 obviousness analysis as related to new chemical compounds. *Eisai v. Dr. Reddy's,* 533 F.3d 1353 (Fed. Cir. 2008). The court stated that "[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable". *Id* at 1359. The court further stated that "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in

general, begins with reasoned identification of a lead compound. *Teva* cannot create a genuine issue of material fact on obviousness through the unsupported assertion that compounds other than landsoprazole might have served as lead compounds". *Id.* A very recent case *Teva* further affirmed *Takeda* and *Eisai* as to the 103 obviousness standard. *Proctor & Gamble v. Teva*, CAFC 2008-1404, -1405, -1406 (Fed. Cir. 2009).

Here, the chemical art of the instant application is both unpredictable and vast. The Examiner's generalized assertion that "[o]ne having ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole" (Office action, third paragraph, page 9) is simply unsupported by the teachings of the cited references. These references, either alone or in combination, fail to identify the right compound as the lead compound for further modifications. Moreover, the references also fail to provide any suggestion or motivation to make the particular molecular modifications necessary to arrive at the instant compounds.

Compounds of the instant claim 1 (hereinafter, "Instant Compounds") have the following general structure:



,

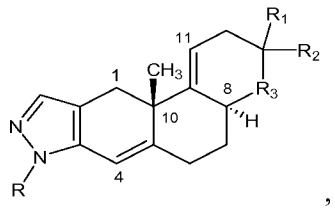
wherein …

with the proviso that when Y_2 is hydrogen, Y_3 is –C(O)-R^{15}, R^{15} is C_{1-6}alkyl and X is –C(O) then R^{10} is not C_{1-6}alkyl, and

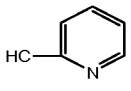
with the proviso that when Y_2 is –C(O)-R^{15}, Y_3 is hydrogen, R^{15} is C_{1-6}alkyl and X is –C(O) then R^{10} is not C_{1-6}alkyl, and

with the proviso that when Y_2 and Y_3 are both hydrogen, X is a bond and R^{10} is HET, then said HET is defined as a 5-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N,…

Instant Compounds are different from those disclosed by Kumar. Kumar generally discloses glucocorticoid-like compounds with diverse structure features on the C- and D-ring. (Kumar, Title and Abstract) The closest compounds disclosed by Kumar appear to be compounds 8-10 in Table 1 having the following general structure:



,

wherein R_3 is  (Compound 8), CHAc (Compound 9) or $C(CO_2Et)_2$ (Compound 10). (Kumar, Table 1, page 3281)

As can be seen, Instant Compounds differ from Compound 8 of Kumar, wherein the substitution at the R_3 position is a 6-membered HET, as claim 1 requires that "when Y_2 and Y_3 are both hydrogen, X is a bond and R^{10} is HET, then said HET is defined as a 5-membered aromatic or non-aromatic monocyclic ring containing 1-3 heteroatoms selected from O, S and N". (Emphasis added for better illustration)

Moreover, Kumar also fails to provide any suggestion or motivation to select Compound 8 as the lead compound and make the necessary modifications to arrive at the Instant Compounds. Additionally, Kumar does not in any way suggest that a 5-membered HET ring should be used to replace the 6-membered pyridine ring at the R_3 position.

Instant Compounds also differ from Compound 9 and Compound 10 of Kumar, wherein the substitutions at the R_3 position are Ac (–C(O)-CH_3) and $(CO_2Et)_2$, respectively, as claim 1 requires that "when Y_2 is hydrogen, Y_3 is –C(O)-R^{15}, R^{15} is C_{1-6}alkyl and X is –C(O) then R^{10} is not C_{1-6}alkyl", and "that when Y_2 is –C(O)-R^{15}, Y_3 is hydrogen, R^{15} is C_{1-6}alkyl and X is –C(O) then R^{10} is not C_{1-6}alkyl". (Emphasis added for better illustration)

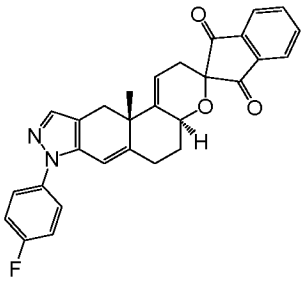
Kumar further fails to suggest that Compound 9 and Compound 10 be selected as lead compounds. These two compounds were mentioned among several compounds that possess affinities to the glucocorticoid receptor that approximate that of a reference standard:

> … Despite these structural changes, 4, 5, 9, 10, 12a, 13, and 14 bound to the glucocorticoid receptor with an affinity which approximated that of the reference standard 6-a-methylprednisolone. …

(Kumar, Abstract, page 3278) Compounds 4, 5, 12a, 13 and 14 are vastly different from the Instant Compounds as they all have oxygen at the R_3 position instead of carbon of the Instant Compounds. (Kumar, Table 1, page 3281)

Nothing in Kumar suggests that compounds 9 and 10 are superior to compounds 4, 5, 12a, 13 and 14 and thus should be picked as the lead compounds. In fact, Kumar appears to

suggest that compound 4, which has the following structure, may be superior to compounds 9-12 with respect to potency as this reference states the following (emphasis added):



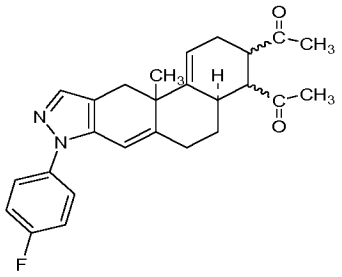
(compound 4)

> The indantrione adduct 4 exhibited a profound effect on all four parameter at low doses. In comparison with 6-a-methylprednisolone 20, adduct 4 was about 5 times less potent as an anti-inflammatory agent but considerably more potent as an adrenal suppressant. In a side-by-side assay, 4 was 17 … times as potent as 20 as a suppressant of adrenal weight and 2 … times as potent as a thymolytic agent as 20. Compound 4 is apparently also significantly more catabolic than 20. …
>
> The activity exhibited by compounds 9-12 was not notable with respect to potency …

(Kumar, last paragraph on the left hand column - last paragraph on the right hand column, page 3281; middle of left column, page 3278) Thus, a skilled artisan would probably select compound 4 (over Compounds 9 and 10 and other disclosed compounds) as the lead compound for further modifications in view of the above disclosure of Kumar.

Therefore, Instant Compounds are not obvious over Kumar as this reference fails to provide any suggestion or motivation to pick Compound 8, 9 or 10 of Kumar as the lead compound and then modify these compounds in the particular manner to arrive at the Instant Compounds.

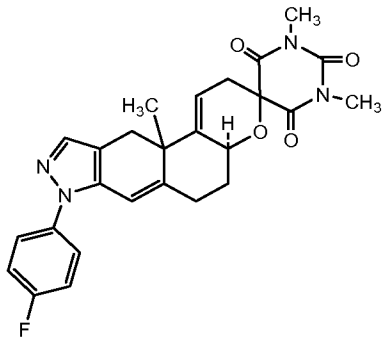
Instant Compounds also are different from those disclosed by Schane. Schane generally discloses 6 nonsteroidal phenylpyrazole compounds that have significant glucocorticoid and anti-inflammatory activities. (Schane, Abstract) The closest compound disclosed by Schane has the following structure:



(Schane, Figure 2, WIN 45164, page 173; hereinafter, "Compound 45164")

Instant Compounds differ from Compound 45164 as claim 1 requires that "when Y_2 is hydrogen, Y_3 is –C(O)-R^{15}, R^{15} is C_{1-6}alkyl and X is –C(O) then R^{10} is not C_{1-6}alkyl", and "that when Y_2 is –C(O)-R^{15}, Y_3 is hydrogen, R^{15} is C_{1-6}alkyl and X is –C(O) then R^{10} is not C_{1-6}alkyl".

Moreover, Schane also fails to provide any suggestion or motivation to select Compound 45164 as the lead compound and make the necessary molecular modifications to arrive at the Instant Compounds. Schane contains no suggestion or motivation that Compound 45164 should be selected as the lead compound. In fact, while all six disclosed compounds have potent glucocorticoid activity in the rat (Schane, first full paragraph, page 182), another compound, 46510 which has very different structure from Compound 45164 as shown below, ranked the most potent in 3 out of 4 activity assays and a close second in the fourth assay where 45164 ranked first.



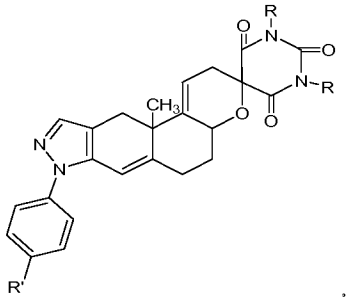
(Compound 46510)

(Schane, Figure 1, page 172; Table 1, page 176; Table 2, page 184)

Thus, a skilled artisan would not be motivated to select Compound 45164 over 46510 as the lead compound. Additionally, Schane does not in any way suggest that the methyl group of Compound 45164 at the R^{10} position should be modified to a non-C_{1-6}alkyl group.

Therefore, Instant Compounds are not obvious over Schane as this reference fails to provide any suggestion or motivation to select compound 45164 as the lead compound and then modify this compound in the particular manner to arrive at the Instant Compounds.

Instant Compounds further are different from those disclosed by Bell. Bell generally discloses polycyclic fused pyrazole compounds and their use as anti-inflammatory agents. (Bell, column 1, lines 11-15) Compounds of Bell generally have the following structure:



(Bell, Summary of the Invention, column 1, lines 45-65)

It can be seen that compounds of Bell have vastly different structure from the Instant Compounds as the Bell compounds have a D ring that is heterocycle which has spiro-connection to another 6-membered ring. There is simply no suggestion or motivation in Bell to modify these compounds in the particular manner required to arrive at the Instant Compounds.

For the same reasons as presented above, claim 22 also is not obvious over the cited references.

Accordingly, Applicants respectfully request withdraw of the §103(a) rejections and allowance of claim 1, its dependent claims 2-4, 11-21, 23 and 29-30, and claim 22.

In view of the foregoing remarks, Applicants respectfully request reconsideration of the pending claims and reexamination of the application. Timely allowance of the pending claims is respectfully requested.

The Examiner is invited to contact the undersigned attorney at the telephone number provided below if such would advance the prosecution of the instant application. Applicants believe no additional fees are due, but the Commissioner is authorized to charge any fees required in connection with this Response from Merck Deposit Account No. 13-2755.

Respectfully submitted,

By /Yong Zhao, Reg. # 57014/
Yong Zhao
Reg. No. 57,014
Attorney for Applicants

MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-7338

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